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Title: Attenuated glomerular arginine transport prevents hyperfiltration and induces HIF-1α in the pregnant uremic rat.

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Background: Pregnancy worsens renal function in females with renal failure (CRF) through an unknown mechanism. Reduced nitric oxide (NO) generation induces renal injury. Arginine transport by cationic amino acid transporter-1 (CAT-1), which governs endothelial NO generation, is reduced in both renal failure and pregnancy.

Research Hypothesis: We hypothesize that attenuated maternal glomerular arginine transport promotes renal damage in CRF pregnant rats

Aims: To link between the changes in glomerular arginine uptake velocities and renal damage in the pregnant uremic rat.

Methods: Arginine transport, NO generation, eNOS, CAT-1, and PKC alpha protein expression was studied in sham operated rats, pregnant rats. Pregnant rats subjected to 5/6 nephrectomy as a model of renal failure with and without administration of L-arginine in the drinking water.

Results: In uremic rats, pregnancy induced a significant decrease in glomerular arginine transport and c-GMP generation (a measure of NO production) compared to CRF or pregnancy alone and these effects were prevented by L-arginine. While CAT-1 abundance was unchanged in all experimental groups, PKCα, phosphorylated PKCα (CAT-1 inhibitor), and phosphorylated CAT-1 were significantly augmented in CRF, pregnant, and pregnant CRF animals, phenomena which were prevented by co-administrating L-arginine. α-tocopherol (PKC inhibitor) significantly increased arginine transport in both pregnant and CRF pregnant rats, effects which were attenuated by ex vivo incubation of glomeruli with PMA (a PKC stimulant). Renal histology revealed no differences between all experimental groups. Inulin and p-aminohippurate clearances failed to augment and renal cortical expression of HIF-1α significantly increased in CRF pregnant rat, findings which were prevented by arginine.

Discussion: These studies suggest that in CRF rats, pregnancy induces a profound decrease in glomerular arginine transport, through post translational regulation of CAT-1 by PKCα, resulting in attenuated NO generation. These events provoke renal damage manifested by upregulation of renal HIF-1α and loss of the ability to increase GFR during gestation.

Conclusions: The pathogenesis of the accelerated decline in renal function during pregnancy in women with chronic renal failure involved a decrease in NO generation due to attenuation of glomerular arginine transport. These events can be prevented by administration of L-arginine.

Key words: Arginine transport, nitric oxide, pregnancy, renal failure
Publications associated with the project: